

### **REMARKS/ARGUMENTS**

Claims 4-6 are currently pending in the application.

Claims 1-3 and 7-29 have been withdrawn by the Examiner as being directed to non-elected subject matter. Applicants reserve the right to present this subject matter in a co-pending application.

Claims 4-6 have been amended herein for clarity, to replace “NO” with “free NO” (see, *inter alia*, Example 4, pages 47-48 and Figure 4 of the originally filed application).

These amendments are supported by the application as originally filed, and do not constitute new matter. Support is shown in parentheses, above. Entry of these amendments is respectfully requested.

### **Restriction Requirement**

The Examiner has deemed the restriction/election requirement proper and has withdrawn claims 1-3 and 7-29 from further consideration (Office Action, pages 2-3). Claims 4-6 are currently pending in the case.

### **35 U.S.C. §102(b) - Jia**

Claim 4 has been rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Jia et al. (1996, *Nature* 380:221-226; “Jia”). According to the Examiner, Jia reports the addition of oxyhemoglobin and S-nitrosoglutathione or S-nitrosocysteine to produce S-nitrosohemoglobin (Office Action, page 4). The Examiner states that S-nitrosoglutathione and S-nitrosocysteine contain nitric oxide (“NO”), and the reported methods thereby anticipate the claimed invention. *Id.*

Applicants respectfully traverse this rejection. As presented herein, claim 4 encompasses methods of using free NO with oxyhemoglobin to produce compositions comprising S-nitrosohemoglobin (see, *inter alia*, page 25, lines 13-21; Example 4, pages 47-48; and Figure 4

of the application as originally filed). Jia does not teach or suggest at least these aspects of the claimed invention.

Jia reports the use of S-nitrosoglutathione and S-nitrosocysteine (Figure 1D and page 222, top left column), but these molecules are distinguished from free NO. The nitroso groups of S-nitrosoglutathione and S-nitrosocysteine are covalently bonded to larger molecules, while free NO is not. The covalently attached moieties of S-nitrosoglutathione and S-nitrosocysteine are understood to be nitrosonium ions, not free NO.

Moreover, Jia reports that the addition of free NO to oxyhemoglobin produces methemoglobin (Hb(Fe<sup>III</sup>)) rather than S-nitrosohemoglobin (SNO-Hb(Fe<sup>II</sup>)O<sub>2</sub>); Figure 1B and page 222, top left column). Compare this with instant claim 4. S-nitrosohemoglobin and methemoglobin are known in the field to be dramatically different molecules (see below).

In contrast, the instant application demonstrates that free NO can successfully be combined with oxyhemoglobin to produce S-nitrosohemoglobin (e.g., in compositions; see, *inter alia*, Example 4, pages 47-48 and Figure 4 of the application as originally filed). These results are novel and unexpected in view of Jia and others in the art.

Prior to the instant case, it was universally believed that free NO combined with hemoglobin to produce methemoglobin, which destroyed NO bioactivity (see, *inter alia*, page 14, lines 10-16 of the originally filed application). Yet, in working examples, Applicants demonstrate that free NO can be used to produce S-nitrosohemoglobin and preserve critical NO function (see, *inter alia*, Examples 4, 6, and 7, pages 47-48 and 49-53; Figures 4, 7, and 8 of the application as originally filed).

It is well established that a reference cited under 35 U.S.C. §102 must teach each and every aspect of the claimed invention. *Verdegall Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631 (Fed. Cir. 1987); MPEP §§706.02 and 2131. The identical invention must be shown in the cited reference, with complete details as set forth in the claims. *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236 (Fed. Cir. 1989).

Here, Jia does not teach or suggest that free NO can be added to oxyhemoglobin to

produce S-nitrosohemoglobin. Jia uses different reactants (S-nitrosoglutathione and S-nitrosocysteine) and obtains different product (methemoglobin) compared to the claimed methods. Thus, Jia does not anticipate the subject matter of claim 4 presented herein. Withdrawal of this rejection is respectfully requested.

### **35 U.S.C. §102(e) - Stamler**

Claims 5-6 have been rejected under 35 U.S.C. §102(e) as allegedly being anticipated by Stamler et al. (U.S. Patent No. 6,153,186; "Stamler"). According to the Examiner, Stamler reports the addition of oxygenated erythrocytes and S-nitrosocysteine to produce intraerythrocytic S-nitrosohemoglobin (Office Action, page 4). The Examiner states that S-nitrosocysteine is an NO donor, and the reported methods thereby anticipate the claimed invention. *Id.*

Applicants respectfully traverse this rejection. As presented herein, claims 5-6 encompass methods of using *free NO* with oxygenated erythrocytes to produce compositions comprising intraerythrocytic S-nitrosohemoglobin (see, *inter alia*, page 25, lines 13-21; Example 4, pages 47-48; and Figure 4 of the application as originally filed). Stamler does not teach or suggest at least these aspects of the claimed invention.

Stamler reports the use of S-nitrosocysteine (Example 6), but this molecule is distinguished from free NO. The nitroso group of S-nitrosocysteine is covalently bonded to a larger molecule, while free NO is not (see also, above). The covalently attached moiety of S-nitrosocysteine is known to be nitrosonium ion, not free NO.

Further, Stamler reports that the addition of free NO to oxyhemoglobin produces methemoglobin rather than S-nitrosohemoglobin (Example 1(B)). Compare this with instant claims 5-6. S-nitrosohemoglobin and methemoglobin are known to be chemically and functionally distinct molecules.

As indicated above, it was previously believed that free NO combined with hemoglobin to produce methemoglobin, which halted NO bioactivity (see, *inter alia*, page 14, lines 10-16 of the originally filed application). However, Applicants have shown that free NO can be used to

produce S-nitrosohemoglobin and maintain NO function (see, *inter alia*, Examples 4, 6, and 7, pages 47-48 and 49-53; Figures 4, 7, and 8 of the application as originally filed).

It is understood that an anticipatory reference must teach each and every aspect of the claimed invention. *Verdegall Bros.*, 814 F.2d at 631; MPEP §§706.02 and 2131. Here, Stamler does not teach or suggest that free NO can be added to oxyhemoglobin to produce S-nitrosohemoglobin. Stamler uses different reactant (S-nitrosocysteine) and obtains different product (methemoglobin) compared to the claimed methods. Thus, Stamler does not anticipate the subject matter of claims 5-6 presented herein. Withdrawal of this rejection is respectfully requested.

### CONCLUSION

Favorable action on the merits is respectfully requested. If there are any questions regarding this Response, the Examiner is encouraged to contact the undersigned at the telephone number provided below. While Applicants believes that no additional fees are required, the Commissioner is authorized to charge any additional fees that may be due, or to credit any overpayment, to the undersigned's account, Deposit Account No. 50-0311, Reference No. 28195-518 (Customer Number: 35437).

Respectfully submitted,

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